International Journal of Gynecology and Obstetrics (2006) **94** (Supplement 1), S81–S88

International Journal of
GYNECOLOGY
& OBSTETRICS

www.elsevier.com/locate/ijgo

CHAPTER 8

HPV vaccines

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KEYWORDS
Cervical cancer;
Vaccination;
Human papillomavirus

Abstract Vaccines to prevent infection with high-risk human papillomaviruses (HPV) will help protect women against cervical cancer, and some are likely to be available within the next year. One vaccine, a quadrivalent vaccine against HPV types 6, 11, 16 and 18 and known as Garadsil® (Merck & Co., Inc), was approved by the Federal Drug Administration (FDA) for the prevention of cervical cancer, cervical cancer precursors and vulval and vaginal cancer precursors associated with HPV 16 and 18 in June 2006. In addition, the vaccine has been approved for the prevention of genital warts and low grade cervical lesions e.g. cervical intraepithelial neoplasia1. The main vaccines components are recombinant viral capsid proteins assembled into virus-like particles and alum-based adjuvants. If given before HPV infection, the vaccines, which induce HPV type-specific, virus-neutralizing antibodies, have proven safe and highly effective at preventing HPV infection and its clinical consequences, including high-grade cervical lesions. Their use should not immediately alter existing screening programs for cervical cancer, however. Because they incorporate only the 2 HPV types most commonly associated with cervical cancer (HPV-16 and HPV-18), they can only prevent about 70% of cervical cancers. Vaccines to treat existing HPV infection are under development but are unlikely to become clinically available in the near future.

1. Introduction

The major goal of immunization against human papillomavirus (HPV) infection is to reduce the incidence of anogenital cancer, which vaccination can achieve by inducing immunity against the "high-risk" genotypes of HPV, thereby preventing persistent infection with these HPV types. A further goal of immunization might be to prevent HPV-associated anogenital warts. Two distinct types of vaccine against HPV are under development, one to prevent infection and the other to treat existing infection (Table 1).

The vaccines to prevent infection made available in 2006 will only incorporate 2 high-risk types of HPV, HPV-16 and HP-V18. These two genotypes are involved in the etiology of approximately 70% of cervical cancers. Thus vaccines against these two types are unlikely to be able to prevent the other 30% of cervical cancers associated with other high-risk types of HPV. Specific therapeutic vaccines, or immunotherapeutics, to treat existing HPV infection are not likely to be available for several years, although nonspecific immunotherapeutics such as imiquimod are currently available.

0020-7292/$ – see front matter

Table 1 Prophylactic and therapeutic HPV vaccines

Characteristic	Immunization to prevent HPV infection	Immunotherapy to eliminate HPV infection
Available in the clinic	In 2006	After 2010
Use	Prevention of infection and consequent disease in young women (and men?)	Treatment of existing HPV infections (screened or unscreened)
Delivery	3 immunizations over 6 months, preferably prior to onset of sexual activity	Not yet known
Duration of protection	>5 years (may be much longer)	Not yet established
Coverage of HPV type	Initially , HPV-16, HPV-18 (cancer) and HPV-6, HPV-11 (genital warts)	Studies currently focused on HPV-16
Antigen	Virus-like particles (L1 capsid protein)	Viral nonstructural proteins (E2, E4, E6, and E7)
Adjuvant	Alum with or without other immune stimulants	Various experimental adjuvants
Mechanism of action	Neutralizing antibody	Cytotoxic T cells
Safety	Established in young women regardless of current HPV status	Still to be determined
Cross protection	Possible for some HPV types	Not expected

2. Vaccines to prevent infection with HPVs

2.1. Prophylactic vaccines produce type-specific antibodies

Preclinical studies in dogs, cattle, and rabbits have shown that antibody, induced by immunization with inactivated papillomavirus virions and targeted to neutralizing conformational epitopes on papillomavirus virions, is sufficient to prevent infection with the corresponding type of papillomavirus. Vaccines to prevent infection with genital genotypes of HPV have been developed by 2 companies. Merck & Co. (Rathway, New Jersey) has developed Gardasil®, which incorporates HPV types 6, 11, 16, and 18 and which received approval for clinical use from the Federal Drug Administration (FDA) in the USA in June 2006. The second vaccine has been developed by GlaxoSmithKline (GSK) Biologicals (Rixensart, Belgium), called Cervarix®, which incorporates HPV-16 and HPV-18 (Table 2). The production of inactivated HPVs is not practical in vitro, as the viruses cannot be grown in continuous cell culture. The HPV vaccines currently under trial are therefore based on virus-like particles (VLPs) (Figure 1), produced by expressing L1, the major capsid protein of HPV, using recombinant DNA technology in yeast or in insect cells. Because the VLPs preserve the structure of the native virus, they resemble the virus physically and induce serological responses cross-reactive with infectious virus particles; but since they contain no genetic information, they are them-

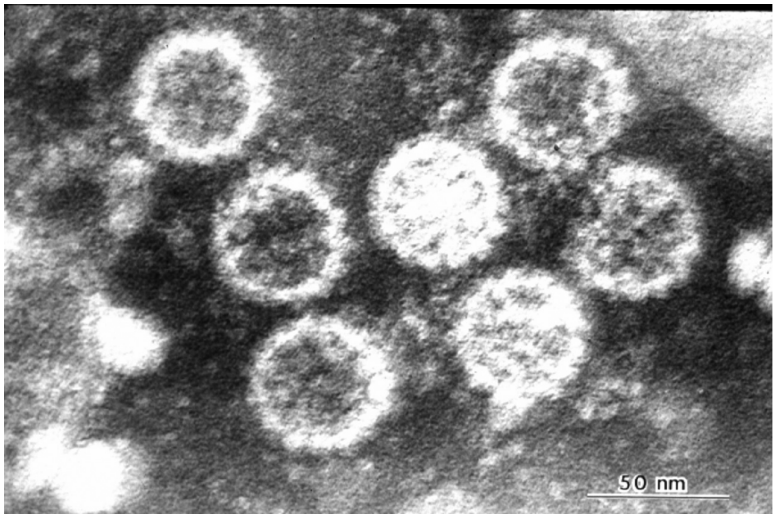

Figure 1 HPV virus-like particles (diameter, 50 nm) assembled from the HPV-6 L1 capsid protein expressed in Sf21 insect cells and purified by density gradient centrifugation. The scanning electron microscopy inset shows a 50-nm scale bar.

Table 2 Summary outcome of interim analysis of three Phase II trials of HPV prophylactic vaccines*

First author	HPV types Adjuvant (μg VLPs)	Product/ Company	Delivery frequency (subject age range)	Follow-up (months post 3rd vaccine)	Number/ arm (age range)		Persistent HPV (any site) (*n*)		Clinical abnormalities (*n*)		HPV type reported
					Vacc	Pl	Vacc	Pl	Vacc	Pl	
Koutsky [3]	16 (40) Alum	Merck	0, 2, 6 m (16–25)	17.4 40	768[a] 755	765 750	0[b] 7	41 111	0[d] 0	9 24	16 16
Harper [4]	16 (20) 18 (20) AS04	Cervarix GSK	0, 1, 6 (15–25)	21	366[c]	355	0 0	13 4	1[e] 1	20 11	16 18
Villa [5]	6 (20) 11 (40) 16 (40) 18 (20) Alum	Gardasil Merck	0, 2, 6 (16–23)	30	244[f]	250	0/214[g] 3/199 1/224	16/209 21/198 9/224	0	3 CIN, 3 genital warts	6/11 16 18

* Reprinted with permission from [7].
[a] According to protocol efficacy analysis – HPV 16 seronegative at day 0 and HPV 16 DNA PCR negative till month 7, on study at month 7, and no protocol violation.
[b] Includes two or more positive tests for HPV16 DNA or a single positive test at the last recorded visit.
[c] According to protocol efficacy analysis – HPV 16/18 seronegative at day 0 and HPV 16/18 DNA PCR negative at 6 m, on study at month 7 and no protocol violation.
[d] Cytological abnormalities for this study reported as CIN1 or greater, and on an according to protocol basis.
[e] Cytological abnormalities for this study reported as ASCUS or greater, and on an intention to treat basis.
[f] According to protocol efficacy analysis for patients without protocol violation – patients with past infection were included but each patient was analysed for vaccine efficacy only for those HPV types for which they were seronegative at day 0 and HPV DNA PCR negative till month 7.
[g] Denominator is patients at risk for this HPV type (i.e. seronegative at day 0 and PCR negative at month 7 with at least one follow-up visit).

selves noninfectious. Currently available HPV virus-like, particle-based vaccines are conventional vaccines designed to produce virus-neutralizing antibody and hence protect against infection with the relevant virus types. There is currently no standardization of assays for serological HPV antibody testing to enable comparisons between studies using different assay methodologies, but an international standard for HPV-16 antibody testing is currently under development by the World Health Organization (WHO) [1].

2.2. Prophylactic vaccine safety is established

Extensive phase 1 clinical trials of HPV virus-like particle-based vaccines with or without adjuvant have established that these are safe in humans, with no systemic adverse effects [2]. Cervarix® and Gardasil® contain small amounts of antigen (20–40 μg) and alum-based adjuvants to give optimal antibody responses following 3 intramuscular administrations over 6 months. No greater reactogenicity at the administration site is demonstrated with these vaccines than with any other alum-containing vaccines, and vaccine recipients experience little more local reactogenicity than placebo recipients. Cervarix® also incorporates monophosphoryl lipid A, which, from prior studies of this adjuvant, may result in greater immunogenicity and/or greater local reactogenicity than vaccines containing alum alone. After 3 administrations, Cervarix® and Gardasil® induce substantial levels of antibody in virtually 100% of young women, with measurable antibody in most women following a single administration.

2.3. Clinical trials show efficacy of HPV vaccines against infection and HPV-associated anogenital disease

Several randomized, placebo-controlled, blinded phase 2 clinical trials of virus-like particle-based vaccines have been published, each conducted in young women at risk for HPV infection but free of infection at recruitment as determined by HPV DNA status and serologic evaluation for HPV (Table 2) [7]. The first randomized, placebo-controlled efficacy study was of a vaccine based on HPV-16 VLPs alone. Subsequent studies have reported on vaccines based on HPV-16 and HPV-18 VLPs (Cervarix®) or HPV types 6,11,16, and 18 VLPs (Gardasil®). These trials have each shown complete protection in vaccine recipients against new and persisting infections with HPVs of the types incorporated in the vaccines, with substantial rates of infection in the placebo recipients

Table 3 Interim analysis of a phase 3 study (FUTURE 2) of a quadrivalent HPV prophylactic vaccine*

Treatment	Vaccine		Placebo	
	No. of participants	No. of CIN 2/3 cases	No. of participants	No. of CIN 2/3 cases
ATP	5301	0	5258	21
MITT	5736	1	5776	36

Abbreviations: ATP, according to protocol; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; MITT, modified intention to treat.
* Adapted from [9].

[3–6,8]. Vaccine efficacy in these trials was assessed in patients immunized according to protocol and still free of infection at the completion of immunization, with infection defined as disease with 1 positive HPV DNA test result, 2 positive HPV DNA test results, or 1 positive HPV DNA test result on the last occasion when the patient was seen. Using one of the less stringent definitions of infection, a single positive test for HPV DNA, some infections were observed in immunized women and the vaccines were about 90% effective in those immunized according to protocol. Vaccine efficacy in these trials was slightly less using a modified intention to treat analysis, where patients were counted if they were given at least 1 immunization and infections were counted if they were first detected after 30 days of the first immunization.

Two phase 3, randomized, placebo-controlled trials of the efficacy of Gardasil®, Females United to Unitерally Reduce Endo/Ectocervical Disease (FUTURE) 1 and FUTURE 2 [12], have been conducted and some of their results announced at conferences (Tables 3 and 4). The aggregated data are available on the US Food and Drugs Administration Website (http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222b-index.htm). These studies, using protocols similar to those of the phase 2 study involving about 5000 women per arm, examined the ability of the vaccine to prevent HPV infection and warts (FUTURE 1) [10] and premalignant HPV lesions (CIN2/3, VIN, and AIN) (FUTURE 2). The vaccine proved 100% effective at preventing both CIN 2/3 and external genital disease, including genital warts, in the study subjects whereas a substantial number of lesions was seen in the controls. Thus, there is level 1 evidence that HPV VLP-based vaccines are effective not only at preventing HPV infection but also at preventing the clinical consequences of such infection in women not infected at the time of immunization.

Papillomaviruses of different genotypes are, by and large, serologically distinct. Yet, a cross-reactivity between HPV-6 and HPV-11 has been well described, and there are suggestions of lesser cross-reactivity between other genital HPV types, particularly between HPV-18 and HPV-45 and between HPV-16 and HPV-31. Data from one vaccine study [6] show protection by an HPV16/18 vaccine (Cervarix®) against infection with HPV-45, the HPV type most closely related to HPV-18, and possible protection against HPV-31. Most HPV types share only limited conformational epitopes against which host-protective neutralizing antibody can be directed, and that study showed no evidence of significant protection against other HPV genotypes.

Immunity following vaccination is long-lasting, as assessed by serum antibody titer and by protection against HPV infection in the clinical trials reported to date. Initial titers of antibody in immunized study subjects are on average 10- to 50-fold higher than those seen following natural infection, and follow-up data on these subjects demonstrate an expected initial decline in serum antibody titer. Antibody titers well above those associated with

Table 4 Interim analysis of a phase 3 study (FUTURE 1) of a quadrivalent HPV prophylactic vaccine*

Treatment	Vaccine		Placebo	
	No. of participants	No. of warts, VIN, and VAIN cases	No. of participants	No. of warts, VIN, and VAIN cases
ATP	2261	0	2279	40
MITT	2620	3	2628	59

Abbreviations: ATP, according to protocol; VIN, vulval intraepithelial neoplasia; VAIN, vaginal intraepithelial neoplasia; MITT, modified intention to treat.
* Adapted from [10].

natural infection are, however, observed for more than 5 years, and protection against infection is also observed for at least 5 years [6,8]. Further, antibody levels do not appear to decline after the first 2 years, suggesting that there may be a natural boosting of antibody responses, perhaps as a consequence of repeated viral challenge. As no breakthrough infections have been demonstrated in optimally immunized women, it is not yet possible to say what minimum level of antibodymight be protective against infection.

3. Issues concerning the optimal deployment of HPV prophylactic vaccines

3.1. Age of immunization and duration of protection

Reports of efficacy studies of the HPV vaccines under commercial development conducted with women aged between 16 and 25 years, as well as bridging studies of immunogenicity conducted with boys and girls aged between 9 and 15 years, are available at: http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222b-index.htm), and Schwartz and colleagues reported on an efficacy study with women aged between 26 and 49 years [11] . All studies show that the vaccine is immunogenic across a wide range of ages, but the strongest immune responses were observed in prepubertal children. These findings reflect the involution of the thymus at puberty and the lesser ability to mount new immune responses thereafter — as has been observed with other vaccines, to which antibody responses are generally lower with increasing age. Moreover, as their age increases, women are at a lower risk of acquiring new HPV infections, and therefore are at a lower risk that a new infection would progress to cancer. Consequently, community vaccination strategies will be of decreasing benefit for the prevention of cervical cancer irrespective of antibody titer if they target older age groups for immunization. It may be indicated to vaccinate individual women older that the age range for which universal vaccination is recommended, if they are at risk of being exposed to new infections with high-risk HPV.

It is unlikely that conventional protein/alum adjuvant vaccines would have an adverse impact on pregnancy, and data from the phase 3 trials show no increase in adverse fetal outcomes in vaccine recipients who became pregnant during these trials compared with placebo recipients who also became pregnant. Nevertheless, as with all new drugs for which adequate reproductive toxicity data are not available, pregnancy or planned pregnancy should be a contraindication to vaccine use.

Most vaccines designed to induce antibody synthesis are optimally given to young children, as humoral immunity is generally better induced in children than in adults and exposure to infections is common in childhood. For the HPV vaccine, a balance between higher antibody titer following immunization and waning immunity with time in the absence of exposure to infection will determine an optimal age for immunization to ensure maximum protection against acquisition of high-risk genital HPV infection. The increased immunogenicity of the current vaccines in prepubertal children suggests that a strong case could also be made for routine immunization in the 0- to 2-year-old age group, with a booster between the ages of 10 and 12 years once appropriate safety and immunogenicity data are available. Of course, the long interval between immunization and demonstrable efficacy may discourage this approach initially.

3.2. Immunization of boys and men

Most HPV vaccine efficacy studies reported to date have been conducted in women only, as women are at much greater risk than men of acquiring anogenital cancer as a result of a high-risk HPV infection. As demonstrated by an herpes simplex virus type 2 vaccine currently under development, it is not a foregone conclusion that a vaccine for an anogenital infection effective in women will be equally effective in men [13]. Eventhough direct evidence of the effect of the HPV vaccines on the transmission of high-risk genotypes in men would be desirable to inform appropriate decisions about deployment of these vaccines, it will be very difficult to obtain. Therefore, the efficacy in men of the HPV vaccines for the prevention of potentially infectious lesions induced by high-risk HPV will likely be inferred from studies in men on the effectiveness of the quadrivalent HPV vaccine in preventing visible genital warts. Presuming that reasonable efficacy is observed, vaccine cost and vaccine availability will be the major determinants of whether any immunization strategy designed to prevent cervical cancer will include men. As a significant part of the burden of HPV-associated malignancy is at sites other than the cervix, including anal cancer, tonsillar cancer, and some other epithelial tumors, vaccination against HPV may have benefits extending well beyond the female cervix.

Recent data however on the immunogenicity of the quadrivalent vaccine in males and females aged 9—15 years have been presented [14]. This placebo controlled randomized trial of 1781 sexually-naïve

children showed that seroconversion rates at month 7 among per protocol vaccine recipients among both genders were ≥99.5% for all 4 vaccine types. Geometric mean titers and seroconversion rates in boys were non-inferior those in girls. At 18 months ≥92% of subjects remained seropositive. These data suggest that the efficacy of the vaccine in preventing HPV infection in males is likely to be equivalent to the efficacy demonstrated in females.

3.3. HPV vaccine effectiveness in immunocompromized individuals

Vaccines are generally less effective in immunocompromized individuals, including pregnant women, the elderly, the malnourished, and those with immune systems damaged by infection (e.g., HIV, measles, and malaria) or treatment (e.g., with corticosteroids or chemotherapy), although substantial immunity can be produced despite these problems, as demonstrated for many of the vaccines from WHO's Expanded Vaccine Initiative. Bridging data on HPV vaccine immunogenicity and field effectiveness in groups likely to be immunocompromized will therefore be necessary to inform development of appropriate vaccine programs for these groups. Pregnant women represent a special group, and while there are no a priori reasons to avoid immunization with this vaccine in pregnancy, further data on safety and in pregnancy is likely to be accumulated only through unintended administration to women not aware of their pregnancy at the time of immunization.

3.4. Testing for prior HPV infection as a determinant of need for vaccination

A negative result to an HPV antibody test is an unreliable marker of the lack of a prior HPV infection. HPV antibody assays are technically difficult, and are neither licensed for clinical use nor available commercially. HPV DNA tests currently licensed for clinical use are designed to have optimal sensitivity for detecting high-risk infections associated with high-grade cervical lesions, and would be less than optimal for detecting incident HPV infection. Therefore, there is no justification at present for screening a woman for HPV DNA or for HPV type-specific antibody prior to deciding whether she should receive HPV immunization, unless such testing is part of a properly designed research protocol or of a screening program for cervical cancer risk.

3.5. Effects of the vaccine on already infected individuals

Data from the many women already infected with relevant viral genotypes who were recruited for clinical trials of HPV vaccines have established the short-term safety of these vaccines. These trials may further reveal whether immunization has any effects, harmful or beneficial, on HPV infection in immunized individuals currently or previously infected with HPV — although preliminary data are not supportive of a significant beneficial effect of immunization on those already infected. The primary purpose of the HPV vaccines currently under development is to induce the synthesis of antibodies against conformational determinants of the HPV virion, and incorporating alum to the vaccine enhances an antibody-dominated immune response. Conversely, the immune response likely to clear virus infection is characterized by cytotoxic and helper T cells, and alum-based adjuvants are not particularly effective at inducing such responses. As virus-infected cells do not display conformationally correct viral capsid proteins, it is likely that the current vaccines will have little effect on existing HPV infection. It may be, however, that the induced antibodies may reduce the infectiousness of lesions already shedding HPV virions, either for other anatomical sites in the infected individual or for recipients of the infection.

3.6. Vaccine genotype coverage and impact on current screening programs

More than 95% of anogenital cancers can be attributed to infection with one of the 10 high-risk HPVs. HPV-16 dominates and causes about 50% of all cervical cancers worldwide, but to control cervical cancer effectively vaccines will need to incorporate more high-risk HPV genotypes than the 2 currently incorporated. Because of the relative scarcity of infection with these types, however, clinical trials will likely be able to only discover whether high-titer, type-specific antibody is induced against the newly incorporated types. Thus, there is a strong mandate to show that antibody (of a particular titer or other in vitro characteristic) is a good surrogate marker for protection, as has been the case with other vaccines.

Given the limited coverage of HPV genotypes in the HPV vaccines currently in clinical trials, it is critical to maintain the screening and treatment programs in place for cervical cancer and precancers (cervical intraepithelial neoplasia [CIN] 2/3), particularly where these programs are effective. It will be necessary to ensure that health care professionals

and the public understand the requirement for continued screening in vaccinated women, at least until the impact of abnormalities detected by screening is understood. The frequency of abnormal cervical smears requiring follow-up or treatment will likely be reduced by about 70% among immunized women, and this, together with the reduced risk of acquiring genital warts, will be the major benefit of vaccination in a screened population.

The substantially reduced rate of abnormal cervical smears will affect training and quality assurance programs in cytopathology, however, and thus have an impact on the delivery of screening programs. Both the interval for screening and the nature of the screening test may change; and automated HPV DNA testing with likely follow cytologic evaluation, rather than the reverse, because it may be more achievable and more cost-effective in a community with a high immunization rate.

In the developing world, and where screening programs do not yet exist, cost-benefit analysis and practical feasibility will determine whether and in what way vaccination and screening programs can be introduced, separately or together, to most effectively reduce the risk of cervical cancer now and in the future (see Chapter 10). The answers to these questions will have a substantial influence on the education programs that will be required to enable governments to make informed choices about vaccine introduction in their countries.

4. Vaccines to treat existing infection with HPV

Persistent infection with high-risk anogenital HPVs is common, with 2% of infections persisting after 5 years from the time infection is detected. Clearance is immunologically mediated, as individuals immunosuppressed by drugs or HIV infection are much more likely to develop persistent infection than individuals without immunosuppression. As the risk of a persistent HPV infection proceeding to cancer is high, it would be desirable to develop immunotherapy that would enhance the immune response to HPV infection for those whose immune system cannot itself clear infection. Virus infection is generally cleared by killer (cytotoxic) T cells directed against peptides derived from viral proteins and presented on the surface of virus-infected cells by MHC class I molecules. Generally, among peptides derived from virus proteins, some will dominate among others, and many of these proteins will most likely be well represented.

Currently there are no licensed vaccines designed to induce or enhance specific cytotoxic T cell responses in humans, and the data from preclinical models are too limited to suggest that such vaccines — with the available adjuvant and antigen presentation systems — are practical for target epithelial cells. The best results to date for therapeutic vaccines in humans have been obtained using live viral vectors such as adenovirus to deliver the relevant target antigens. A considerable number of potential systems have been used to deliver HPV antigens (particularly E6 and E7 proteins of HPV-16) to the immune system. While these have proven safe and generally immunogenic, the evidence for induction or substantial enhancement of cytotoxic T cells is limited [2]. The efficacy of specific immunotherapy in phase 1, open-label studies of such vaccines in humans has been anecdotal. While further phase 1 and phase 2 studies are in progress, any practical clinical application of specific immunotherapeutics to eliminate persisting HPV infection must be regarded as several years in the future.

Disclosure of conflict of interest

Ian Frazer is an inventor named on patents concerning VLP technology for HPV vaccines described in this chapter and may benefit financially from the sale of these vaccines.

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